UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,223	01/04/2006	Mathaeus Dejori	1454.1658	1087

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STAAS & HALSEY LLP
SUITE 700
1201 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER
WHALEY, PABLO S

ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

PTOL-90A (Rev. 04/07)

<table>
<tr><td rowspan="2">Office Action Summary</td><td>Application No.
10/563,223</td><td>Applicant(s)
DEJORI ET AL.</td></tr>
<tr><td>Examiner
PABLO WHALEY</td><td>Art Unit
1631</td><td></td></tr>
</table>

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
   Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**.   2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) <u>25-47</u> is/are pending in the application.

    4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) <u>25-47</u> is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on <u>04 January 2006</u> is/are: a)☒ accepted or b)☐ objected to by the Examiner.

    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

    a)☒ All   b)☐ Some * c)☐ None of:

      1.☒ Certified copies of the priority documents have been received.

      2.☐ Certified copies of the priority documents have been received in Application No. _____ .

      3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

    * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
   Paper No(s)/Mail Date <u>04/05/2006 , 01/04/2006</u>.

4) ☐ Interview Summary (PTO-413)
   Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____ .

U.S. Patent and Trademark Office
PTOL-326 (Rev. 08-06)   Office Action Summary   Part of Paper No./Mail Date 20090429

DETAILED ACTION

Status of Claims

Claims 25-47 are pending.

Claims 25-47 are rejected.

Claims 1-24 are cancelled in the amendment filed 01/04/2006.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on German Application

No. 10330280 filed July 4, 2003. The certified copy was filed in the instant application on 01/04/2006.

Drawings

Drawings filed 01/04/2006 have been accepted.

Information Disclosure Statement

The information disclosure statement filed 04/05/2006 has been considered in full.

The information disclosure statement filed 01/04/2006 has been considered in full.

Claim rejections - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly
> claiming the subject matter which the applicant regards as his invention.

Claims 26-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 26-37 recite "the selected gene." There is lack of antecedent basis for this limitation. This

is sufficient basis for genes of the regulatory network.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 25-47 are rejected under 35 U.S.C. 101 because these claims are drawn to non-statutory subject matter. These claims are rejected for the following reasons.

The claimed subject matter is directed to a process and program for performing a process for analyzing a regulatory genetic network. A claimed process is statutory under 35 U.S.C. 101 if: (1) it is tied to a particular machine or apparatus of statutory subject matter under 35 U.S.C. §101 (i.e. a machine, manufacture, or composition of matter), or (2) it transforms a particular article into a different state or thing (In re Bilski, 88 USPQ2d 1385 Fed. Cir. 2008; In re Comiskey, Fed. Cir., No. 2006-1286).

Regarding the required tie to a particular machine or apparatus, the claimed subject matter is not limited to a particular apparatus or machine. In the instant case, the claimed process provides gene expression rate data, generates patterns using said data, and compares data. To qualify as a statutory process, the claims should require use of a machine within the steps of the claimed subject matter or require transformation of an article to a different state or thing. Insignificant data gathering in the claimed subject matter are not considered sufficient to convert a process that otherwise recites only mental steps into statutory subject matter. Preamble limitations directed to using a network are not considered sufficient to convert a process that otherwise recites only mental steps into statutory subject matter. The applicants are cautioned against introduction of new matter in an amendment.

Regarding the transformation test, the claimed subject matter does not recite a physical transformation of matter. For example, while claim provides gene expression rate data, the claim does not require any physical gene expression assays [See In re Grams, 12 USPQ2d 1824 (Fed Cir. 1989)]. This rejection could be overcome by amendment of the claims to recite a step wherein an article is reduced to a different state or thing (e.g. physical assay), [See also In re Abele, 684, F.2d at 908-909, CCPA, 1982]. The applicants are cautioned against introduction of new matter in an amendment.

In addition, claim 47 is non-statutory because they read on a signal. In particular, the claims are drawn to a computer readable medium storing a program. A review of the specification does not show any limiting definitions or examples of computer readable media such the claims exclude an embodiment of computer readable media that is information in a signal. Therefore, the embodiment of the claims reads on non-statutory subject matter (In re Nuijten 84 USPQ2d 1495 (2007)). The applicants may overcome the rejection by amendment of the claims to be limited to physical forms of computer readable media described in the specification, or if no description exists for physical computer readable media, by presenting a statement that the claims do not read on embodiments that are not physical computer readable media that are conventional in the art. The applicants are cautioned against introduction of new matter in an amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25, 26, 28, 29, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spirtes et al. (Proceedings of the Atlantic Symposium on Computational Biology and Genome Information and Technology, 2001, p. 1-5), in view of Heckman et al. (Machine Learning, 1995, Vol. 20, p.197-243, IDS filed 04/05/2006).

A review of the specification does not provide a limiting definition for "gene expression patterns of a regulatory genetic network" but does suggest that gene expression patterns represent the state of the regulatory genetic network of a cell [0008, 009, 0029]. For purposes of examination, this limitation is interpreted to be the collection of nodes and connectors that represent genes and their interactions.

Spites teaches Bayesian regulatory genetic network models for the analysis of gene expression data. In particular, nodes represent genes and causal connectors represent regulatory interactions between genes [Sections 1 and 2]. The method presents genes as distinct gene expression rates using directed acyclic graphs [Section 1, Col. 1, para. 2], and provides a variable rate value "r(1)" (i.e. a predetermined gene expression rate) for two selected genes in a regulatory network of genes [Fig. 4 and Section 4.7]. Based on the value of this gene expression rate, two different gene expression patterns in a regulatory network are possible [Fig. 4]. Spites teaches causal networks comprising Bayesian networks and directed acyclic graphs [Section 2, Section 2.1, Fig. 1]. Spirtes shows inferring causal network structure from gene expression data [Section 4.1], which is a teaching for a gene expression pattern for a genetic network. Spirtes presents several well known methods of searching microarrays to select subsets of genes that are causally interacting [Section 4.1]. Spirtes shows that most Bayesian networks have assumed data is normal or discrete [Section 4.4].

Spirtes does not teach comparing the resulting gene expression pattern with a predetermined gene expression pattern of the regulatory genetic network, as in claim 25.

Heckerman teaches Bayesian networks using a combination of prior knowledge and statistical data [Abstract]. In particular, Heckerman teaches a learning algorithm that compares patterns resulting from a prior network with patterns resulting from networks from database analysis [p.198, para. 1 and 2, and Fig. 1]. A scoring parameter (i.e. Bayes factor) is calculated to compare networks that is based on statistical code to determine the probability [p.198-199 and Fig. 1], which shows comparing using statistical code. In addition, the learning network adapts by adding nodes and connectors to the network

[Fig. 1(d)]. The motivation would have been to provide learning algorithms that corrected the prior knowledge of the user, as suggested by Heckerman [p.198, para. 2]. Heckerman teaches network properties for representing discrete states [Fig. 2].

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Spirtes by comparing the resulting gene expression pattern with a predetermined gene expression pattern of the regulatory genetic network, as in claim 25, since Heckerman teaches a learning algorithm that compares patterns resulting from a prior network with patterns resulting from networks from database analysis [p.198, para. 1 and 2, and Fig. 1]. The motivation would have been to provide learning algorithms that corrected the prior knowledge of the user, as suggested by Heckerman [p.198, para. 2].

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Spirtes by training gene expression patterns to adapt the nodes and the connectors of the causal network, as in claim 31, since Heckerman teaches a learning algorithm that adapts by adding nodes and connectors to the network [Fig. 1(d)]. The motivation would have been to provide learning algorithms that corrected the prior knowledge of the user, as suggested by Heckerman [p.198, para. 2]. Heckerman teaches network properties for representing discrete states [Fig. 2].

Claims 25-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spirtes et al. (Proceedings of the Atlantic Symposium on Computational Biology and Genome Information and Technology, 2001, p. 1-5), in view of Heckman et al. (1995, IDS filed 04/05/2006), as applied to claims 25, 26, 28, 29, and 30, above, and further in view of Friedman et al. (Journal of Computational Biology, 2000, Vol. 7, No. ¾, p.601-620, IDS filed 01/04/2006).

Spirtes and Heckerman make obvious a method and program for analyzing regulatory genetic networks, as set forth above. In addition, Heckerman teaches a scoring parameter (i.e. Bayes factor) is calculated to compare networks that is based on statistical code to determine the probability [p.198-199 and Fig. 1], which shows comparing using statistical code. In addition, the learning network adapts by adding nodes and connectors to the network [Fig. 1(d)]. The motivation would have been to provide learning algorithms that corrected the prior knowledge of the user, as suggested by Heckerman [p.198, para. 2]. Heckerman teaches network properties for representing discrete states [Fig. 2].

Spirtes and Heckerman do not specifically teach including a gene expression rate reflecting an assumption of a gene defect, as in claim 26.

Spirtes and Heckerman do not teach including discrete gene states, as in claim 31.

Spirtes does not teach comparing gene expression patterns using a static method or a statistical code as a measure of distance, as in claim 32.

Spirtes does not teach training gene expression patterns to adapt the nodes and the connectors of the causal network, as in claim 33.

Friedman teaches Bayesian networks for analyzing gene expression data [Abstract, p.607, Section 3.1]. In particular, Friedman shows discretizing gene expression data into three states: normal, underexpressed, and overexpressed [p.610, Section 3.5]. The motivation would have been to select multinomial models by accounting for gene expression rates compared to a control, as suggested by Friedman [p.610, Section 3.5].

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method made obvious by Spirtes and Heckerman by including a gene expression rate reflecting an assumption of a gene defect, as in claim 26, since Friedman shows modeling of knockout and over-expressed mutants with causal networks [p.618, last para.]. The motivation would have been to

provide a method that learns from both observational and interventional data, as suggested by Friedman [p. 618, last para.].

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Spirtes by comparing gene expression patterns using a static method or a statistical code as a measure of distance, as in claim 32, since Heckerman teaches scoring parameters for comparing networks that is based on statistical information [p.198-199 and Fig. 1], which suggests comparing using statistical code. The motivation would have been to provide learning algorithms that corrected the prior knowledge of the user, as suggested by Heckerman [p.198, para. 2].

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method made obvious by Spirtes and Heckerman by including a gene expression rate reflecting an assumption of a gene defect, as in claim 26, since Friedman teaches Bayesian networks for analyzing gene expression data [Abstract, p.607, Section 3.1] and discretizing gene expression data into three states: normal, underexpressed, and overexpressed [p.610, Section 3.5]. The motivation would have been to select multinomial models by accounting for gene expression rates compared to a control, as suggested by Friedman [p.610, Section 3.5].

Claims 25-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spirtes et al. (Proceedings of the Atlantic Symposium on Computational Biology and Genome Information and Technology, 2001, p. 1-5), in view of Heckerman et al. (1995, IDS filed 04/05/2006), and in view of Friedman et al. (2000, IDS filed 01/04/2006), as applied to claims 25-33, above, and further and further in view of Yeoh et al. (Cancer Cell, 2002, Vol. 1, p.133-143, IDS filed 04/05/2006).

Spirtes, Heckerman, and Friedman make obvious a method and program for analyzing regulatory genetic networks, as set forth above.

Spirtes, Heckerman, and Friedman do not teach determining predetermined and training gene expression patterns using DNA microarrays, as in claim 34.

Spirtes, Heckerman, and Friedman do not teach determining predetermined and training gene expression patterns for a diseased cell, as in claims 35, 36, and 37.

Yeoh teaches learning algorithms applied to gene expression data sets obtained from microarrays [p.137-138, Col. 1] for classification of leukemia cells. In particular, learning algorithms are applied to training and test gene expression patterns for specific genes [p.137, Col. 2, Table 1].

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method made obvious by Spirtes, Heckerman, and Friedman by determining predetermined and training gene expression patterns for a diseased cells using microarrays, as in claims 34, 35, 36, and 37, since Yeoh teaches learning algorithms applied to gene expression data sets obtained from microarrays [p.137-138, Col. 1] and applied to training and test gene expression patterns for specific genes [p.137, Col. 2, Table 1]. The motivation would have been to identify leukemia genes or patients at risk of treatment failure, as suggested by Yeoh [p.137, Col. 1, p.138, Col. 1].

Claims 25-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spirtes et al. (Proceedings of the Atlantic Symposium on Computational Biology and Genome Information and Technology, 2001, p. 1-5), in view of Heckerman et al. (1995, IDS filed 04/05/2006), in view of Friedman et al. (2000, IDS filed 01/04/2006), and in view of Yeoh et al. (2002, IDS filed 04/05/2006), as applied to claims 25-37, above, and further in view of De la Fuente (2nd Int. Conf. on Systems Biology, 2001, pp. 213–221).

Spirtes, Heckerman, Friedman, and Yeoh make obvious a method and program for analyzing regulatory genetic networks, as set forth above. In addition, Friedman teaches a procedure for identifying

dominant genes using genetic network simulations [p.613]. In addition, Yeoh teaches a learning algorithm for classifying leukemia genes [p.137 and Table 1 and Fig. 4], which shows identifying disease genes and cancer genes. Yeoh also teaches the analysis of expression patterns obtained from patients who have been treated (i.e. the effect of a medicament) and patients still with leukemia [p.138, Col. 2, and Fig. 4]

Spirtes, Heckerman, Friedman, and Yeoh do not teach determining a plurality of predetermined gene expression rates for selected genes, as in claims 38, 39, 44.

Spirtes, Heckerman, Friedman, and Yeoh do not teach simulating an effect of a medicament, as in claims 45 and 46.

De la Fuente teaches a method and program for analysis of a regulatory genetic network of cells based on perturbations of gene transcription rates (i.e. gene expression rates) [Abstract, p.214, Col. 1]. In particular, a plurality of rate parameters are determined for specific genes in the regulatory network [p.214, Col. 1, p.215, Col. 2, Fig. 1]. These rates are perturbed using microarray data, which shows abnormal gene expression rates, and this process is repeated until new regulatory networks have been constructed [p.215, Col. 2, Table 1]. These models are used to represent several different scenarios [p.215, Section 3] and to monitor gene expression in response to perturbations or where genes have mutated [p.218, Col. 1, Section 4, para. 2].

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method made obvious by Spirtes, Heckerman, Friedman, and Yeoh by determining a plurality of predetermined gene expression rates for selected genes, as in claims 38, 39, and 44, since De la Fuente determines a plurality of rate parameters for specific genes in the regulatory network [p.214, Col. 1, p.215, Col. 2, Fig. 1]. The motivation would have been to model several different biological scenarios and control regulatory strength, as suggested by De la Fuente [p.215, Section 3, and p.216, Col. 2].

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method made obvious by Spirtes, Heckerman, Friedman, and Yeoh by simulating an effect of

a medicament based on comparing of gene expression patterns, as in claims 45 and 46, since Yeoh also teaches the analysis of expression patterns for patients who have been treated (i.e. the effect of a medicament) along with patients that are still suffering from leukemia [p.138, Col. 2, and Fig. 4], and since Friedman teaches interventional modeling [p.618, last para.] and since De la Fuente teaches gene expression monitoring in response to simulated perturbations of gene expression rates [p.215, Col. 2, Table 1, p.218, Col. 1, Section 4, para. 2]. The motivation would have been to use genetic network models for developing new treatments for disease, as suggested by Spirtes [Introduction, Col. 1].

Provisional Obviousness-Type Double Patenting Rejection

The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R. 1.321 (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. 3.73(b).

Claim 25-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of co-pending Application No. 10/307997 in view of Spirtes and Heckerman. Claims 1-5 of co-pending Application No. 10/307997 do not require a step for comparing gene expression patterns of a regulatory genetic network. However, this limitation would have been obvious to one of ordinary skill in the art since Spirtes and Heckerman make obvious a method and

program for comparing gene expression patterns of regulatory genetic networks, as set forth above. The motivation would have been to provide learning algorithms that corrected the prior knowledge of the user, as suggested by Heckerman [p.198, para. 2]. This is a <u>provisional</u> obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached at 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Pablo S. Whaley

Patent Examiner

Art Unit 1631

/PW/

/John S. Brusca/

Primary Examiner, Art Unit 1631